What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naive Children (Updated August 11, 2011)

Panel's Recommendations
• Combination therapy, including either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone, is recommended for initial treatment of HIV-infected children **(AI)**.
• The goal of therapy in treatment-naive children is to reduce plasma HIV RNA levels to below the limits of quantitation of ultrasensitive assays and to preserve or normalize immune status **(AI)**.
• Antiretroviral (ARV) drugs initiated for chemoprophylaxis of mother-to-child (MTCT) transmission of HIV should be discontinued in infants who are identified as HIV infected **(AI)**.
• ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive children (**AII** infants; **AIII** children).

General Considerations

More than 20 ARV drugs are approved for use in HIV-infected adults and adolescents; 17 have an approved pediatric treatment indication and 15 are available as a pediatric formulation or in a capsule size suitable for pediatric use. ARV drugs fall into several major drug classes: NRTIs, NNRTIs, PIs, entry inhibitors (including fusion inhibitors and CCR5 antagonists), and integrase inhibitors. Information on drug formulation, pediatric dosing, and toxicity for the individual drugs and detailed information on drug interactions can be found in Appendix A: Pediatric Antiretroviral Drug Information. Over time, new drugs and drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles will likely become available, which will increase treatment options for children.

Combination antiretroviral therapy (cART) with at least three drugs from at least two drug classes is recommended for initial treatment of HIV-infected infants, children, and adolescents because it provides the best opportunity to preserve immune function and delay disease progression[3-6]. The goal of antiretroviral therapy (ART) is to maximally suppress viral replication, preferably to undetectable levels, for as long as possible while preserving and/or restoring immune function and minimizing drug toxicity. Combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic response, and delays development of virus mutations that confer resistance to the drugs being used[5-7].

If an infant is confirmed as HIV infected while receiving chemoprophylaxis to prevent mother-to-child transmission (MTCT) of HIV, prophylactic ARV drugs should be discontinued promptly and treatment initiated with a combination regimen of at least three drugs. Zidovudine may be included as a component of the treatment regimen if zidovudine drug-resistance mutations are not detected.

Treatment-naive children with perinatal HIV infection can have drug-resistant virus, either by acquisition of a resistant virus from their mother or by developing resistance while receiving ARV prophylaxis. Thus, ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive children. In infants receiving prophylactic ARV drugs for prevention of perinatal transmission of HIV, ARV drug-resistance testing can be performed at the same time as confirmatory HIV testing or when

prophylactic ARV drugs are discontinued. Drug-resistant virus has been identified in 6%–16% of ARV-naive adults and 18% of behaviorally infected adolescents with recent infection in the United States and Europe[8-12]. Data from children in resource-rich regions are limited. In a study in New York State, genotypic drug resistance was identified in 12% of 91 HIV-infected infants born from 1998 to 1999 and in 19% of 42 infants born from 2000 to 2001[13-14]. Detection of resistance in the infants was not significantly associated with a history of maternal and infant ARV prophylaxis. Similarly, following initiation of treatment, mutations associated with drug resistance were detected in 24% of 21 infants at a median age of 9.7 weeks. Most of the mutations were not associated with maternal/infant prophylaxis regimens and resistant virus was persistently archived in the resting CD4 cell reservoir in all the infants[15]. Thus, the prevalence of infants infected with ARV drug-resistant virus may be increasing and may not necessarily be predicted by the drug prophylaxis regimen received by the mother. In a study in Africa, infants, regardless of whether they were exposed to single-dose nevirapine as part of prophylaxis to prevent HIV MTCT, had higher rates of virologic failure on nevirapine-based regimens compared with lopinavir/ritonavir-based regimens[1-2]. For ARV-naive children beyond infancy, limited available data do not demonstrate that resistance testing before initiation of therapy correlates with greater success of initial ART[16]. Nevertheless, because the prevalence of resistance in HIV-infected children is sufficiently high and based on expert opinion, the Panel recommends resistance testing before initiation of therapy in all treatment-naive children and use of resistance testing results to select the initial combination therapy[17]. Recommendations on resistance testing in HIV-infected adults are similar.

Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Table 8)

Panel's Recommendations

- The Panel recommends initiating antiretroviral therapy (ART) in treatment-naive children using one of the following agents (in alphabetical order) plus a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone combination:
  - For children ≥42 weeks of postmenstrual age and postnatal ≥14 days of age: lopinavir/ritonavir **(AI)**
  - For children age ≥3 years: efavirenz **(AI*)**
  - For children age ≥6 years: atazanavir/ritonavir **(AI*)**.
- The Panel recommends the following preferred dual-NRTI backbone combinations:
  - Abacavir + (lamivudine or emtricitabine) **(AI)**
    - HLA-B*5701 genetic testing should be performed before initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 **(AII*)**.
  - Zidovudine + (lamivudine or emtricitabine) **(AI*)**
  - For adolescents ≥12 years of age and Tanner Stage 4 or 5: tenofovir + (lamivudine or emtricitabine) **(AI*)**.
- Table 8 provides a list of Panel-recommended alternative and acceptable regimens.
- Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**.
- Alternative regimens may be preferred for some patients based on their individual characteristics and needs.

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children

A combination ARV regimen in treatment-naive children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. Regimens should be individualized based on advantages and disadvantages of each combination (see Tables 11–13).

Preferred Regimens	
Children age ≥14 days and <3 years[1]	Two NRTIs ***plus*** LPV/r
Children age ≥3 years	Two NRTIs ***plus*** EFV[2] Two NRTIs ***plus*** LPV/r
Children age ≥6 years	Two NRTIs ***plus*** ATV plus low-dose RTV Two NRTIs ***plus*** EFV[2] Two NRTIs ***plus*** LPV/r
Alternative Regimens	
Children of any age	Two NRTIs ***plus*** NVP[3]
Children age ≥6 years	Two NRTIs ***plus*** DRV plus low-dose RTV Two NRTIs ***plus*** FPV plus low-dose RTV
Regimens for Use in Special Circumstances	
Two NRTIs ***plus*** ATV unboosted (for treatment-naive adolescents age ≥13 years and body weight >39 kg) Two NRTIs ***plus*** FPV unboosted (children age ≥2 years) Two NRTIs ***plus*** NFV (children age ≥2 years) Zidovudine ***plus*** 3TC ***plus*** ABC	
2-NRTI Backbone Options for Use in Combination with Additional Drugs (in alphabetical order)	
Preferred	ABC ***plus*** (3TC ***or*** FTC) (children age ≥3 months) TDF ***plus*** (3TC ***or*** FTC) (adolescents age ≥12 years and Tanner Stage 4 or 5 only) ZDV ***plus*** (3TC ***or*** FTC)
Alternative	ddI ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (adolescents age ≥12 years and Tanner Stage 3) ZDV ***plus*** ABC ZDV ***plus*** ddI
Use in Special Circumstances	d4T ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (adolescents age ≥12 years and Tanner Stage 2)

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Not Recommended or Insufficient Data to Recommend for Initial Therapy	
	ETR-containing regimens EFV-containing regimens for children age <3 years TPV-containing regimens SQV-containing regimens IDV-containing regimens Dual (full-dose) PI regimens Full-dose RTV or use of RTV as the sole PI Unboosted ATV-containing regimens in children age <13 years and/or body weight <39 kg NFV-containing regimens for children age <2 years Unboosted DRV-containing regimens Once-daily dosing of LPV/r, boosted DRV, or boosted or unboosted FPV Triple-NRTI regimens other than ABC + ZDV + 3TC Triple-class regimens, including NRTI plus NNRTI plus PI Regimens with dual-NRTI backbones of ABC + ddI, ABC + TDF, ddI + TDF, and ddI + d4T TDF-containing regimens in children age <12 years or children age ≥12 years and Tanner Stage 1 MVC-containing regimens Rilpivirine-containing regimens RAL-containing regimens T-20-containing regimens

[1] LPV/r should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

[2] EFV is currently available only in capsule form and should be used only in children age ≥3 years who weigh ≥10 kg. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[3] NVP should not be used in postpubertal girls with CD4 count >250 cells/mm^3, unless the benefit clearly outweighs the risk.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; d4T = stavudine; ddI = didanosine; DRV = darunavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TDF = tenofovir; TMC-278 = rilpivirine; TPV = tipranavir; ZDV = zidovudine

Criteria Used for Recommendations

In general, Panel recommendations are based on review of pediatric and adult clinical trial data published in peer-reviewed journals. (The Panel may also review data prepared by manufacturers for Food and Drug Administration [FDA] review and data presented in abstract format at major scientific meetings.) Few randomized, Phase III clinical trials of cART in pediatric patients exist that provide direct comparison of different treatment regimens. Most pediatric drug data come from Phase I/II safety and pharmacokinetic (PK) trials and nonrandomized, open-label studies. In general, even in studies in adults, assessment of drug efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 cell count and HIV RNA levels. The Panel continually modifies recommendations on the optimal initial therapy for children as new data become available, new therapies or drug formulations are developed, and additional toxicities become recognized.

Information considered by the Panel for recommending specific drugs or regimens include:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- The extent of pediatric experience with the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;
- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (e.g., powders), volume of syrups, and pill size and number;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions with other medications.

The Panel classifies drugs or drug combinations into one of several categories as follows:

- ***Preferred:*** Drugs or drug combinations are designated as *preferred* for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies demonstrate that safety and efficacy are suggested using surrogate markers; additional considerations are listed above.
- ***Alternative:*** Drugs or drug combinations are designated as *alternatives* for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared with preferred regimens in terms of more limited experience in children; the extent of antiviral efficacy or durability is less well defined in children or less than a preferred regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.
- ***Use in Special Circumstances:*** Some drugs or drug combinations are recommended for use as initial therapy only in special circumstances, when preferred or alternative drugs cannot be used.
- ***Not Recommended:*** Some drugs and drug combinations are not recommended for initial therapy in children because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism. These drugs and drug combinations are listed in Table 9.
- ***Insufficient Data to Recommend:*** For a number of drugs and drug combinations approved for use in adults, PK or safety data in children are not available or are too limited to make a recommendation on use of the drugs as initial therapy in children. Some of these drugs and drug combinations may be

Table 9. ARV Regimens or Components that Should Never Be Recommended for Treatment of HIV Infection in Children

	Rationale	Exceptions
ARV regimens never recommended for children		
One ARV drug alone (monotherapy)	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV. • 3TC *or* FTC interim "bridging regimen" in special circumstances of children with treatment failure associated with drug resistance and persistent nonadherence.
Two NRTIs alone	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• Not recommended for initial therapy. • For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment.
TDF ***plus*** ABC ***plus*** (3TC ***or*** FTC) as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naive adults	• No exceptions.
TDF ***plus*** ddI ***plus*** (3TC ***or*** FTC) as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naive adults	• No exceptions.
ARV components never recommended as part of an ARV regimen for children		
ATV ***plus*** IDV	• Potential additive hyperbilirubinemia	• No exceptions.
Dual-NNRTI combinations	• Enhanced toxicity	• No exceptions.
Dual-NRTI combinations: • 3TC ***plus*** FTC	• Similar resistance profile and no additive benefit	• No exceptions.
• d4T ***plus*** ZDV	• Antagonistic effect on HIV	• No exceptions.
EFV in first trimester of pregnancy or for sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured	• Potential for teratogenicity	• When no other ARV option is available and potential benefits outweigh risks.
NVP in adolescent girls with CD4 count >250 cells/mm^3 or adolescent boys with CD4 count >400 cells/mm^3	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs the risk.
Unboosted SQV, DRV, or TPV	• Poor oral bioavailablity • Inferior virologic activity compared with other PIs	• No exceptions.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; d4T = stavudine; ddI = didanosine; DRV = darunavir; EFV = efavirenz; FTC = emtricitabine; IDV = indinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; SQV = saquinavir; TDF = tenofovir; TPV = tipranavir; ZDV = zidovudine

appropriate for consideration in the management of the treatment-experienced child, even though they are not recommended for initial therapy in children (see Antiretroviral Treatment Failure in Infants, Children, and Adolescents).

Factors to Consider When Selecting an Initial Regimen

Choice of a regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing. Advantages and disadvantages of each class-based regimen are delineated in detail in the sections that follow and in Tables 10–13. In addition, because ART will need to be administered lifelong, considerations related to the choice of initial ARV regimen should also include an understanding of barriers to adherence, including the complexity of schedules and food requirements for different regimens; differing formulations; palatability problems; and potential limitations in subsequent treatment options should resistance develop. Treatment should only be initiated following assessment and counseling of the caregivers regarding adherence to therapy[3, 18].

Choice of NNRTI- Versus PI-Based Initial Regimens

Preferred regimens for initial therapy include both NNRTI- and PI-based regimens. The selection of an NNRTI- or PI-based regimen should be based on patient characteristics and preferences, results of viral resistance testing, and information cited below.

Recent clinical trial data in children provide some guidance for choosing between an NNRTI-based regimen and a PI-based regimen for initial therapy. P1060 compared a nevirapine-based regimen to a lopinavir-based regimen in HIV-infected infants and children, age 2 to 35 months, in seven African countries. Infants and children in this study were stratified at entry based on either prior maternal or infant exposure to single-dose nevirapine prophylaxis for prevention of mother-to-child transmission (PMTCT) and randomized to receive either zidovudine, lamivudine, and nevirapine or zidovudine, lamivudine, and lopinavir/ritonavir. Among infants and children with prior exposure to nevirapine, 39.6% of children in the nevirapine group reached a study endpoint of death, virologic failure, or toxicity by Week 24 compared with 21.7% of children in the lopinavir/ritonavir group[1]. Among infants and children with no prior nevirapine exposure, 40.1% of children treated with nevirapine met a study endpoint after 24 weeks in the study compared with 18.4% of children who received lopinavir/ritonavir[2]. Additional nonrandomized studies have also indicated that infants exposed to nevirapine in the peripartum period as part of PMTCT strategy had a higher risk of treatment failure because of nevirapine resistance[19-21].

A comparison of a PI-based regimen and an NNRTI-based regimen was also undertaken in HIV-infected treatment-naive children, age 30 days to <18 years, in PENPACT-1 (PENTA 9/PACTG 390). (The study did not dictate the specific NNRTI or PI initiated.) In the PI-based group, 49% of children received lopinavir/ritonavir and 48% received nelfinavir; in the NNRTI-based group, 61% of children received efavirenz and 38% received nevirapine. Efavirenz was recommended only for children age >3 years. After 4 years, 82% of children in both groups had viral loads <400 copies/mL, suggesting that selection of an NNRTI or a PI did not influence outcome. Although the age of participants overlapped somewhat between P1060 and PENPACT-1 (in PENPACT-1 the lowest quartile was age <2.8 years); PENPACT-1 generally enrolled older children[22].

Results of the P1060 study support the recommendation that a PI-based regimen containing lopinavir/ritonavir should be the recommended, preferred initial regimen for children <3 years of age based on superior virologic suppression. However, in both single-dose nevirapine-exposed and -unexposed children in the P1060 study, participants receiving the nevirapine-based regimen demonstrated a better

immunologic response and growth compared with children receiving a lopinavir/ritonavir-based regimen, although these differences did not achieve statistical significance. Similarly, in the NEVEREST study, children switched to a nevirapine regimen showed better immune and growth responses compared with children continuing a lopinavir/ritonavir regimen[23]. Based on these findings, the potential for improved lipid profiles with nevirapine use[23-24], and the poor palatability of liquid lopinavir/ritonavir, liquid nevirapine remains an acceptable alternative for infants not exposed to single-dose nevirapine for PMTCT who cannot tolerate lopinavir/ritonavir.

In children >3 years of age, either an NNRTI-based or a PI-based regimen is acceptable.

NNRTI-Based Regimens (one NNRTI + two-NRTI backbone)

Summary: NNRTI-Based Regimens

Nevirapine and efavirenz both have an approved pediatric indication. Nevirapine is available in a liquid formulation, but efavirenz is not available in a liquid formulation in the United States. Advantages and disadvantages of different NNRTI drugs are delineated in Table 10. Use of NNRTIs as initial therapy preserves the PI class for future use and confers lower risk of dyslipidemia and fat maldistribution than use of some agents in the PI class. Additionally, for children taking solid formulations, NNRTI-based regimens generally have a lower pill burden than PI-based regimens. The major disadvantages of the current NNRTI drugs approved for use in children are that a single viral mutation can confer high-level drug resistance, and cross resistance develops between nevirapine and efavirenz.

In infants, regardless of whether nevirapine is used as part of PMTCT, nevirapine-based regimens demonstrate higher rates of virologic failure compared with lopinavir/ritonavir-based regimens[1-2]. Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all NNRTI drugs, but is most frequent with nevirapine, at least in HIV-infected adults. NNRTIs, similar to PIs, have the potential for interactions with other drugs also metabolized via hepatic enzymes; however, these drug interactions are less frequent with NNRTIs than with boosted PI regimens.

Efavirenz, in combination with two NRTIs, is the preferred NNRTI for initial therapy of children age ≥3 years based on clinical trial experience in children and because higher rates of toxicity have been observed with nevirapine in clinical trials in adults. Results of studies comparing virologic response to nevirapine- versus efavirenz-based regimens in adults are conflicting, and no randomized studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome (SJS) and rare but potentially life-threatening hepatitis[25-26], nevirapine is recommended as an alternative, rather than a preferred, NNRTI for initial treatment of ARV-naive children.

Preferred NNRTI

Efavirenz as preferred NNRTI (AI*): In clinical trials in HIV-infected adults, a PI-sparing regimen of efavirenz in combination with zidovudine and lamivudine was associated with an excellent virologic response; 70% of treated adults had plasma HIV RNA <400 copies/mL at 48 weeks[27]. In randomized controlled trials in treatment-naive adults, efavirenz-treated patients had superior or similar virologic activity compared with patients receiving PI- or triple NRTI-based regimens[28-31]. Clinical trials in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine (see discussion below)[32-36]. In PENPACT-1 (PENTA 9/PACTG 390) subjects receiving efavirenz or nevirapine showed comparable virologic suppression after 4 years[22]. An analysis of children and adults starting first-line ART in Uganda has demonstrated the superiority of an efavirenz-based regimen compared with a nevirapine-based regimen in 222 children and adolescents (mean age, 9.2 years)[37]. Few had received nevirapine as part of a PMTCT regimen.

Efavirenz in combination with two NRTIs or with an NRTI and a PI has been studied in HIV-infected children[38-44]. Results are comparable to those seen in adults. At this time, no pediatric formulation of efavirenz is available in the United States. The appropriate dose of efavirenz for children age <3 years has not been determined; therefore, efavirenz is not recommended for children in this age group. For children ≥3 years of age who are unable to swallow pills, some clinicians recommend breaking open efavirenz capsules and adding the contents to food or liquid. However, because data on the PKs of efavirenz administered in this manner are lacking, this practice is not recommended.

The major limitations of efavirenz are central nervous system (CNS) side effects in both children and adults; reported side effects include fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some patients the symptoms may persist or occur months after initiating efavirenz. In several studies, the incidence of such side effects was correlated with efavirenz plasma concentrations and occurred more frequently in adult patients with higher levels of drug[45-48]. In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Rash may also occur with efavirenz treatment; it is generally mild and transient but appears to be more common in children than adults[42, 44]. Additionally, efavirenz taken by a pregnant woman during the first trimester of pregnancy is potentially teratogenic to the fetus (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Efavirenz is not recommended for initial therapy in adolescent females who are sexually active and may become pregnant unless adequate contraception can be ensured.

Alternative NNRTI

Nevirapine as alternative NNRTI (AI): Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown ARV efficacy in a variety of combination regimens (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information)[49]. Nevirapine in combination with two NRTIs or with an NRTI and a PI has been studied in HIV-infected children[50-52].

In a large adult trial (2NN trial), although virologic efficacy was comparable between nevirapine and efavirenz (plasma HIV RNA <50 copies/mL at 48 weeks in 56% of those receiving nevirapine vs. 62% of those receiving efavirenz), serious hepatic toxicity was more frequent in the nevirapine arm than the efavirenz arm (hepatic laboratory toxicity in 8%−14% of those on nevirapine, compared with 5% on efavirenz)[36]. Other studies in adults have indicated potentially increased risk of hepatic toxicity with nevirapine-based compared with efavirenz-based regimens[53]. Additionally, data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 counts and in women, particularly women with CD4 counts >250 cells/mm^3 and men with CD4 counts >400 cells/mm^3. A more recent study including 820 women in Kenya, Zambia, and Thailand demonstrated that hepatic toxicity was associated with elevated baseline liver function tests (LFTs) and not CD4 count at the time of nevirapine initiation[54]. In the published literature, hepatic toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults[51-52, 55]. In an FDA review of 783 HIV-infected pediatric patients, there was only 1 case of hepatitis, which was reported in a 17-year-old child; there was no evidence of a serious hepatic event associated with nevirapine use in any child prior to adolescence[55]. A recent report of 1,434 children in Malawi receiving treatment with a nevirapine-based regimen noted that only 0.14% of the children discontinued the regimen because of hepatic toxicity[56]. In contrast, skin reactions and HSRs associated with nevirapine use have been reported in children[57]. The safety of substituting efavirenz for nevirapine in patients who have experienced nevirapine-associated hepatic toxicity is unknown. Efavirenz use in this situation has been well tolerated in the very limited number of patients in whom it has been reported but this substitution should be attempted with caution[58].

Because of the higher potential for toxicity and possibly an increased risk of virologic failure, nevirapine-based regimens are considered an alternative rather than the preferred NNRTI in children age ≥3 years. In children <3 years, nevirapine is considered an alternative NNRTI because of increased risk of virologic failure. Even if not exposed to nevirapine as part of PMTCT, infants on nevirapine-based regimens had higher rates of virologic failure compared with infants on lopinavir/ritonavir-based regimens [1-2, 19, 59]. However, infants treated with nevirapine showed a trend for greater improvements in both immunologic status and growth[1].

A recent study randomized infants exposed to nevirapine who had achieved viral suppression for an average of 9 months using a lopinavir/ritonavir-based therapy as part of a PMTCT regimen to continue the lopinavir/ritonavir regimens or to switch to a nevirapine-based regimen. After 52 weeks of follow up, plasma viremia ≥50 copies/mL (the primary endpoint) occurred less frequently in the switch group compared with the continuing arm. CD4 response was also better in the switch group. However, 20% of the switch group experienced breakthrough viremia (confirmed viral load >1,000 copies/mL) and subsequent analysis demonstrated that failure was associated with higher (>25%) frequencies of pretreatment NNRTI mutations[60]. These findings suggest this strategy may be an option for children in whom standard genotyping before treatment detects no NNRTI mutations and should be undertaken with careful monitoring of viral load[23].

Similar to recommendations in adults, nevirapine also should not be used in postpubertal adolescent girls with CD4 counts >250/mm^3 because of the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk[26]. Nevirapine also should be used with caution in children with elevated pretreatment LFTs.

PI-Based Regimens (PIs [boosted or unboosted] + two-NRTI backbone)

Summary: PI-Based Regimens

Nine PIs are currently approved for use; seven are approved for use in children and have pediatric drug formulations. Advantages and disadvantages of different PIs are delineated in Table 11. Advantages of PI-based regimens include excellent virologic potency, high barrier for development of drug resistance (requires multiple mutations), and sparing of the NNRTI drug class. However, because PIs are metabolized via hepatic enzymes the drugs have potential for multiple drug interactions and may be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to consider in selecting a PI-based regimen for treatment-naive children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly related to metabolic complications), and availability of data in children. (Table 11 lists the advantages and disadvantages of PIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.)

Ritonavir acts as a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme, thereby inhibiting the metabolism of other PIs coadministered with ritonavir. The drug has been used in low doses combined with another PI as a "PK booster," increasing drug exposure by prolonging the half-life of the second, "boosted" PI. Boosted PI-based regimens are commonly used in treatment of adults, but adequate pediatric data are only available for coformulated lopinavir/ritonavir in children age >6 weeks[61] and for atazanavir, fosamprenavir, darunavir, and tipranavir with low-dose ritonavir in children age ≥6 years. Additionally, the use of low-dose ritonavir increases the potential for hyperlipidemia[62] and drug-drug interactions.

The Panel recommends either atazanavir with low-dose ritonavir or coformulated lopinavir/ritonavir as

Table 10: Advantages and Disadvantages of Different NNRTIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children

	Advantages	Disadvantages
General Issues		
NNRTI-based Regimens	**NNRTI Class Advantages:** • Less dyslipidemia and fat maldistribution than PIs. • PI sparing. • Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens.	**NNRTI Class Disadvantages:** • Single mutation can confer resistance, with cross resistance between EFV and NVP. • Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with nevirapine). • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4).
Preferred		
EFV (for children ≥3 years of age who can take capsules)	• Potent ARV activity. • Once-daily administration. • Can give with food (but avoid high-fat meals).	• Neuropsychiatric side effects (bedtime dosing recommended to reduce CNS effects). • Rash (generally mild). • No commercially available liquid. • No data on dosing for children age <3 years. • Teratogenic in primates. Use with caution in adolescent females of childbearing age.
Alternative		
NVP	• Liquid formulation available. • Dosing information for young infants available. • Can give with food.	• Reduced virologic efficacy in young infants, regardless of whether exposed to NVP as part of a PMTCT regimen. • Higher incidence of rash/HSR than other NNRTIs. • Higher rates of serious hepatic toxicity than EFV. • Decreased virologic response compared with EFV. • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of NVP metabolism and is associated with a lower incidence of toxicity. • Twice-daily dosing.
Not Recommended		
EFV (for children age <3 years)	• Potent ARV activity. • Once-daily administration. • Can give with food (but avoid high-fat meals).	• Neuropsychiatric side effects (bedtime dosing recommended to reduce CNS effects). • Rash (generally mild). • No commercially available liquid. • No data on dosing for children age <3 years. • Teratogenic in primates. Use with caution in adolescent females of childbearing age.

Table 10: Advantages and Disadvantages of Different NNRTIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 2 of 2

	Advantages	Disadvantages
Not Recommended		
ETR	• Three or more baseline NNRTI mutations result in a decreased virologic response. • Patients with a history of NNRTI-related rash do not appear to be at increased risk of ETR-related rash.	• Limited data on pediatric dosing or safety. • No pediatric formulation available. • Food effect (should be given with food). • No data in treatment-naive patients. • Multiple drug interactions with PIs and other medications. • Twice-daily dosing. • Skin rash.
Rilpivirine	• Once-daily administration. • Reduced CNS effects compared with EFV.	• No data on pediatric dosing or safety. • No pediatric formulation available. • Higher rate of treatment resistance and cross resistance to the NNRTI class in adults compared with EFV. • Adults with viral loads >100,000 copies/mL) are more likely to experience virologic failure compared with patients with viral loads <100,000 copies/mL.

Key to Acronyms: ARV = antiretroviral; CNS = central nervous system; CYP3A4 = cytochrome P450; EFV = efavirenz; ETR = etravirine; HSR = hypersensitivity reaction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PMTCT = prevention of mother-to-child transmission; SJS = Stevens-Johnson syndrome

the preferred PI for initial therapy in children based on virologic potency in adult and pediatric studies, high barrier to development of drug resistance, excellent toxicity profile in adults and children, availability of appropriate dosing information, and experience as initial therapy in both resource-rich and resource-limited areas. Although lopinavir/ritonavir can be used in children ≥42 weeks postmenstrual age and 14 days of age, at the current time atazanavir with low-dose ritonavir should be used only in children ≥6 years of age. Two additional PIs, darunavir and fosamprenavir, can be considered as alternative PIs for use in children age ≥6 years when used in combination with low-dose ritonavir. Other PIs that can be considered in special circumstances when preferred and alternative drugs are not available or are not tolerated include fosamprenavir without boosting ritonavir in children age ≥2 years, atazanavir without boosting ritonavir in adolescents age ≥13 years and who weigh >39 kg, and nelfinavir in children age ≥2 years. A saquinavir/ritonavir (1,000/100 mg twice daily)-based regimen compared with a lopinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naive adults[63]. The guidelines for adults and adolescents list the saquinavir / ritonavir-based regimen as an acceptable PI-based regimen that should be used with caution as initial therapy[26]. However, saquinavir is not recommended for initial therapy in children because the agent is not available in a pediatric formulation and dosing and outcome data on saquinavir use in children are limited. Although good virologic and immunologic responses have been observed with indinavir-based regimens in adults, the drug is not available in a liquid formulation and high rates of hematuria, sterile leukocyturia, and nephrolithiasis in pediatric patients using indinavir have been reported[64-67]. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults[64, 67]. Therefore, indinavir alone or with ritonavir boosting is not recommended as initial

therapy in children. Additionally, tipranavir is not recommended for initial therapy at the present time because experience with the drug in treatment-naive children is limited.

Because the data on PKs of full-dose dual-PI combination regimens in children (e.g., saquinavir plus co-formulated lopinavir/ritonavir or plus nelfinavir) are limited[68-70], these combinations are not recommended as initial therapy in children.

Preferred PIs

Atazanavir with low-dose ritonavir as preferred PI (for children ≥6 years) (AI*): Atazanavir is a once-daily PI that was approved for use in children >6 years of age in March 2008. It has equivalent efficacy to efavirenz-based and lopinavir/ritonavir-based combination therapy when given in combination with zidovudine and lamivudine in treatment-naive adults[71-72]. Seventy-three percent of 48 treatment-naive South African children achieved viral load <400 copies/mL by 48 weeks when given atazanavir with or without low-dose ritonavir in combination with 2 NRTIs[73]. Among 41 treatment-naive children ages 6–18 years in IMPAACT/PACTG P1020A who received the capsule formulation of atazanavir with or without ritonavir, 68% and 59% achieved viral load <400 copies/mL and <50 copies/mL, respectively, by 48 weeks[74]. When given with low-dose ritonavir boosting, atazanavir achieves enhanced concentrations compared with the unboosted drug in adults and children >6 years of age[75-76] and in ARV-naive adults appears to be associated with fewer PI-resistance mutations at virologic failure compared with atazanavir given without ritonavir boosting[77]. The main adverse effect associated with atazanavir/low-dose ritonavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher with low-dose ritonavir boosting than with atazanavir alone[62].

Lopinavir/ritonavir as preferred PI (AI): In clinical trials in adults, regimens containing lopinavir/ritonavir plus two NRTIs have been found to have potent virologic activity in treatment-naive patients. In a comparative trial of lopinavir/ritonavir versus nelfinavir (both combined with stavudine/lamivudine), lopinavir/ritonavir had superior virologic efficacy compared to nelfinavir (plasma HIV RNA <400 copies/mL in 84% vs. 66% of patients, respectively), and drug-resistant virus in patients with detectable plasma viral load at 48 weeks was detected in none of 51 lopinavir/ritonavir-treated patients, compared with 45% of 43 nelfinavir-treated patients[78-79]. The groups had similar rates of toxicity. Lopinavir/ritonavir has been studied in both ARV-naive and -experienced children and has demonstrated durable virologic activity and low toxicity[1, 7, 80-85]. (See Appendix A: Pediatric Antiretroviral Drug Information for detailed information.) In addition, dosing and efficacy data in infants as young as 4 weeks of age are available[7, 61, 80]. Post-marketing reports of lopinavir/ritonavir-associated cardiac toxicity (including complete atrioventricular [AV] block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death have been reported, predominantly in preterm neonates. These reports have resulted in a change in lopinavir/ritonavir labeling including a recommendation to not administer the combination to neonates until they reach a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. Additionally, although once-daily lopinavir/ritonavir is FDA approved for initial therapy in adults, PK data in children do not support a recommendation for once-daily dosing in children[86-87].

Alternative PIs

Darunavir with low-dose ritonavir as alternative PI (for children age ≥6 years) (AI*): Darunavir combined with low-dose ritonavir is approved for ARV-naive and -experienced adults and for ARV-naive and -experienced children age ≥6 years. In a randomized, open-label trial in adults, darunavir/ritonavir

(800/100 mg once daily) was found to be noninferior to lopinavir/ritonavir (once or twice daily), when both boosted PIs were administered in combination with tenofovir/emtricitabine. Plasma HIV RNA levels were <50 copies/mL in 84% of darunavir/ritonavir recipients and in 78% of lopinavir/ritonavir recipients ($p < 0.001$). Adverse events were also less common in the darunavir/ritonavir group ($p < 0.01$)[88]. No published data exist on the use of darunavir as part of initial treatment in children or the use of once-daily darunavir in children. In a study of treatment-experienced children (6–17 years of age), twice-daily darunavir/ritonavir-based therapy was well tolerated and 48% of the children achieved HIV-1 RNA <50 copies/mL by 48 weeks[89]. Darunavir with low-dose ritonavir is recommended as an alternative initial therapy in HIV-infected children based on data from one study in treatment-experienced children and the finding of high potency and low toxicity in adults. Some experts would only recommend boosted darunavir for treatment-experienced children and reserve its use for patients with PI-resistant mutations. Once-daily dosing of darunavir is not recommended for children.

Fosamprenavir with low-dose ritonavir as alternative PI (for children age ≥6 years) (AI*): Fosamprenavir (the prodrug of amprenavir) is now available in a pediatric liquid formulation and a tablet formulation. Amprenavir is no longer manufactured. In June 2007, fosamprenavir suspension was approved for use in pediatric patients ≥2 years of age. The approval was based on two open-label studies in pediatric patients 2–18 years of age[90-91]. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). There is less pediatric experience with fosamprenavir than with lopinavir/ritonavir. In an adult clinical trial, fosamprenavir with low-dose ritonavir was demonstrated to be noninferior to lopinavir/ritonavir[92]. In children age ≥6 years, fosamprenavir should be used in combination with low-dose ritonavir boosting to ensure adequate drug levels. Data on appropriate dosing of fosamprenavir in combination with low-dose ritonavir in children age <6 years are not available; therefore, this combination cannot be recommended for children in that age group. Once-daily dosing of fosamprenavir is not recommended for pediatric patients.

PIs for Use in Special Circumstances

Atazanavir without ritonavir boosting in children age ≥13 years (BII*): Although unboosted atazanavir is approved for treatment-naive adolescents age ≥13 years who weigh >39 kg and are unable to tolerate ritonavir, data from the ongoing IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (on a mg/m^2 body surface area basis) are required in adolescents than in adults to achieve adequate drug concentrations. (See Appendix A: Pediatric Antiretroviral Drug Information for detailed information on dosing used in IMPAACT/PACTG P1020A.) If using unboosted atazanavir in treatment-naive patients, clinicians should consider using a dual-NRTI combination other than didanosine/emtricitabine because this combination demonstrated inferior virologic response in adults in ACTG 5175[93]. If didanosine, emtricitabine, and atazanavir are used in combination, patients should be instructed to take didanosine and atazanavir at least 2 hours apart, to take atazanavir with food, and to take didanosine on an empty stomach.

Fosamprenavir without ritonavir boosting in children age ≥2 years (BII*): Fosamprenavir without ritonavir boosting has been studied in children age ≥2 years but is only recommended in special circumstances when preferred or alternative PI-based regimens cannot be used.

Nelfinavir for children age ≥2 years (BI*): Nelfinavir in combination with two NRTIs is an acceptable PI choice for initial treatment of children age ≥2 years in special circumstances. The pediatric experience with nelfinavir-based regimens in ARV-naive and -experienced children is extensive, with follow-up in children receiving the regimen for as long as 7 years[94]. The drug has been well tolerated—diarrhea

is the primary side effect of the drug; however, in clinical studies the virologic potency of nelfinavir has varied greatly, with reported rates of virologic suppression of 26%–69% (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Several studies have shown a correlation between nelfinavir trough concentrations and virologic response in treatment-naive pediatric patients[95]. In one such study, virologic response at Week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs (<0.8 mg/L) versus in 80% of children with therapeutic nelfinavir troughs (>0.8 mg/L)[95]. The interpatient variability in plasma concentrations is great in children, with lower levels in younger children[96-101]. The optimal dose of nelfinavir in younger children, particularly in children age <2 years, has not been well defined. In one study, infants required higher doses of nelfinavir (relative to body size) than older children to achieve adequate drug levels[96]. PK parameters in adolescent patients have not been well studied, and some adolescents may require higher nelfinavir doses than those recommended in adults. These data, combined with data in adults showing inferior potency of nelfinavir compared with other PIs and efavirenz, balanced against the advantage of a PI that is not coadministered with low-dose ritonavir for boosting[79, 102-105], make nelfinavir an agent for use in special circumstances in treatment-naive children age ≥2 years and not recommended for treatment of children age <2 years.

The pediatric powder formulation of nelfinavir has a poor acceptance rate when mixed with food or formula, and the PKs of the drug are extremely variable in children. To overcome the problems associated with this formulation, tablets are dissolved in water or other liquids to make a slurry that is then ingested by children unable to swallow whole tablets. Dissolving nelfinavir tablets in water and swallowing whole tablets resulted in comparable PK parameters in a study in adults[106].

Table 11. Advantages and Disadvantages of Different PIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 1 of 4

	Advantages	Disadvantages
General Issues		
PI-based Regimens	**PI Class Advantages:** • NNRTI sparing. • Clinical, virologic, and immunologic efficacy well documented. • Resistance to PIs requires multiple mutations. • Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes).	**PI Class Disadvantages:** • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance. • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4). • Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations. • Poor palatability of liquid preparations, which may affect adherence to treatment regimen.
Preferred		
ATV in combination with low-dose RTV in children age ≥6 years	• Once-daily dosing. • ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).	• No liquid formulation. • Food effect (should be administered with food). • Indirect hyperbilirubinemia common but asymptomatic. • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG).

Table 11. Advantages and Disadvantages of Different PIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 2 of 4

	Advantages	Disadvantages
Preferred		
LPV/r	• Coformulated liquid and tablet formulations. • Tablets can be given without regard to food but may be better tolerated when taken with meal or snack.	• Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone. • Food effect (liquid formulation should be administered with food). • RTV component associated with large number of drug interactions (see RTV). • Should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days. • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG).
Alternative		
DRV in combination with low-dose RTV in children age ≥6 years	• Effective in PI-experienced children when given with low-dose RTV boosting.	• Pediatric data limited to ARV-experienced children. • Pediatric pill burden high with current tablet dose formulations. • No liquid formulation. • Food effect (should be given with food). • Must be given with RTV boosting to achieve adequate plasma concentrations. • Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown. • Cannot administer once daily in children (investigation ongoing).
FPV in combination with low-dose RTV in children age ≥6 years	• Oral prodrug of APV with lower pill burden. • Pediatric formulation available, which should be given to children with food.	• Skin rash. • More limited pediatric experience than preferred PI. • Must be given with food to children. • RTV component associated with large number of drug interactions (see RTV). • Contains sulfa moiety. Potential for cross sensitivity between FPV and other drugs in sulfonamide class is unknown.
Use in Special Circumstances		
ATV (unboosted) in treatment-naive adolescents age ≥13 years and weight >39 kg who are unable to tolerate RTV	• Once-daily dosing. • Less effect on TG and total cholesterol levels than other PIs.	• No liquid formulation. • Food effect (should be administered with food). • Indirect hyperbilirubinemia common but asymptomatic. • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG). • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations. • Unboosted ATV cannot be used with TDF.
FPV (unboosted) in children age ≥2 years	• Oral prodrug of APV with lower pill burden. • Pediatric formulation available. • Can give with food.	• Skin rash. • More limited pediatric experience than preferred PI. • May require boosted regimen to achieve adequate plasma concentrations; PK data to define appropriate dosing not yet available.

Table 11. Advantages and Disadvantages of Different PIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 3 of 4

	Advantages	Disadvantages
Use in Special Circumstances (continued)		
NFV in children age ≥2 years	• Powder formation (for liquid preparation or to be added to food). • Can give with food. • Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate.	• Diarrhea. • Powder formulation poorly tolerated. • Food effect (should be administered with food). • Appropriate dosage for younger children not well defined. • Need for 3 times daily dosing for younger children. • Adolescents may require higher doses than adults. • Less potent than boosted PIs.
Not Recommended		
ATV (unboosted) in children age <13 years and/or weight <39 kg	• Once-daily dosing (age >13 years). • Less effect on TG and total cholesterol levels than other PIs.	• Drug levels low if used without RTV boosting. • No liquid formulation. • Food effect (should be administered with food). • Indirect hyperbilirubinemia common but asymptomatic. • Must be used in caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG). • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations.
IDV (unboosted or boosted)	• May be considered for use as component of a regimen in combination with low-dose RTV in postpubertal adolescents who weigh enough to receive adult dosing.	• Only available in capsule. • Possible higher incidence of nephrotoxicity in children. • Requires 3 times daily dosing unless boosted with RTV. • High fluid intake required to prevent nephrolithiasis. • Food effect (should be taken 1 hour before or 2 hours after food). • Limited pediatric PK data.
RTV (full dose as single PI)	• Liquid formulation. • Can be given with food.	• Poor palatability of liquid (bitter taste). • GI intolerance. • Food effect (should be administered with food). • Large number drug interactions (most potent inhibitor of CYP3A4).
TPV	• Effective in PI-experienced children and adults when given with low-dose RTV boosting. • Liquid formulation.	• Limited data in treatment-naive patients. • Food effect (should be administered with food). • Must be given with RTV boosting to achieve adequate plasma concentrations.

Table 11. Advantages and Disadvantages of Different PIs for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 4 of 4

	Advantages	Disadvantages
Not Recommeded (continued)		
NFV in children age <2 years	• Powder formation (for liquid preparation or to be added to food). • Can give with food. • Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI- containing regimens in older patients where the adult dose is appropriate.	• Diarrhea. • Powder formulation poorly tolerated. • Food effect (should be administered with food). • Appropriate dosage for younger children not well defined. • Need for 3 times daily dosing for younger children. • Adolescents may require higher doses than adults. • Less potent than boosted PIs.
SQV (unboosted or boosted)		• Low bioavailability, should never be used as sole PI. • Limited pediatric PK data; will require boosting with another PI (e.g., RTV) to achieve adequate concentrations. • No liquid formulation. • High pill burden. • Must be taken with food. • Potential for photosensitivity reactions

Key to Acronyms: APV = amprenavir; ARV = antiretroviral; ATV = atazanavir; CYP3A4 = cytochrome P450; DRV = darunavir; ECG = electrocardiogram; FPV = fosamprenavir; GI = gastrointestinal; IDV = indinavir; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; SQV = saquinavir; TDF = tenofovir; TG = triglyceride; TPV = tipranavir

Selection of Dual-NRTI Backbone as Part of Initial Combination Therapy

Summary: Selection of Dual-NRTI Backbone Regimen

Currently, six NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, and emtricitabine) are FDA approved for use in children <13 years of age. Tenofovir is FDA approved for use in adolescents who are ≥12 years of age and weigh ≥35 kg. Dual-NRTI combinations form the "backbone" of combination regimens for both adults and children. Dual-NRTI combinations that have been studied in children include zidovudine in combination with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; and emtricitabine in combination with stavudine or didanosine[18, 40, 94, 100, 107-108]. Advantages and disadvantages of different dual-NRTI backbone options are delineated in Table 12.

Preferred Dual-NRTI Regimens

The dual-NRTI combinations preferred for initial therapy in children are abacavir or zidovudine combined with either lamivudine or emtricitabine.

Zidovudine in combination with either lamivudine or emtricitabine in children (AI*): The most extensive experience in children is with zidovudine in combination with lamivudine. Data on the safety of this combination in children are extensive and the combination is generally well tolerated. The major toxicity associated with zidovudine/lamivudine is bone marrow suppression, manifested as macrocytic anemia

Table 12. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 1 of 2

	Advantages	Disadvantages
Preferred Combinations		
ABC ***plus*** (3TC ***or*** FTC)	• Palatable liquid formulations. • Can give with food. • ABC and 3TC are coformulated as a single pill for older/heavier patients.	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
ZDV ***plus*** (3TC ***or*** FTC)	• Extensive pediatric experience. • ZDV and 3TC are coformulated as single pill for older/heavier patients. • Palatable liquid formulations. • Can give with food. • FTC is available as a palatable liquid formulation administered once daily.	• Bone marrow suppression with ZDV. • Lipoatrophy with ZDV.
TDF ***plus*** (3TC ***or*** FTC) for adolescents ≥12 years of age and Tanner Stage 4 or 5 only	• Resistance slow to develop. • Once-daily dosing for TDF. • Less mitochondrial toxicity than other NRTIs. • Can give with food. • Bone toxicity may be less in postpubertal children. • TDF and FTC are coformulated as single pill for older/heavier patients.	• No pediatric formulation of TDF. • Limited pediatric experience. • Potential bone and renal toxicity. • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV.
Alternative Combinations		
ddI plus (3TC or FTC)	• Delayed-release capsules of ddI may allow once-daily dosing in older children able to swallow pills and who can receive adult dosing along with once-daily FTC. • FTC available as a palatable liquid formulation administered once daily.	• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when compliance is an issue (ddI can be coadministered with FTC or 3TC). • Limited pediatric experience using delayed-release ddI capsules in younger children. • Pancreatitis, neurotoxicity with ddI.
TDF ***plus*** (3TC ***or*** FTC) for adolescents ≥12 years of age and Tanner Stage 3	• Resistance slow to develop. • Once-daily dosing for TDF. • Less mitochondrial toxicity than other NRTIs. • Can give with food. • TDF and FTC are coformulated as single pill for older/larger patients.	• No pediatric formulation of TDF. • Limited pediatric experience. • Potential for bone and renal toxicity. • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.
ZDV ***plus*** ABC	• Palatable liquid formulations. • Can give with food.	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment. • Bone marrow suppression and lipoatrophy with ZDV.
ZDV ***plus*** ddI	• Extensive pediatric experience. • Delayed-release capsules of ddI may allow once-daily dosing of ddI in older children able to swallow pills and who can receive adult doses.	• Bone marrow suppression and lipoatrophy with ZDV. • Pancreatitis, neurotoxicity with ddI. • ddI liquid formulation less palatable than 3TC or FTC liquid formulation. • Food effect (recommended to take ddI 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when compliance is an issue.

Table 12. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Highly Active ARV Combination Regimens for Initial Therapy in Children (see Pediatric Antiretroviral Drug Information Appendix for more information). Page 2 of 2

	Advantages	Disadvantages
Use in Special Circumstances		
d4T ***plus*** (3TC ***or*** FTC)	• Moderate pediatric experience. • Palatable liquid formulations. • Can give with food. • FTC available as a palatable liquid formulation administered once daily.	• d4T associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia. • Limited pediatric experience with d4T plus FTC.
TDF ***plus*** (3TC ***or*** FTC) for adolescents ≥12 years of age and Tanner Stage 2	• Resistance slow to develop. • Once-daily dosing for TDF. • Less mitochondrial toxicity than other NRTIs. • Can give with food. • Bone toxicity may be less in postpubertal children. • TDF and FTC are coformulated as single pill for older/larger patients.	• No pediatric formulation of TDF. • Limited pediatric experience. • Potential bone and renal toxicity. • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.
Not Recommended		
3TC ***plus*** FTC	• None.	• Similar drug structure. • Single mutation (M184V) associated with resistance to both drugs.
d4T ***plus*** ddI	• Has shown antiviral activity in small studies in children. • Although not recommended for initial therapy, it may be considered for use in ARV-experienced children who require a change in therapy.	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis.
TDF-containing regimens in children <12 years of age or children ≥12 years who are Tanner Stage 1	• Resistance slow to develop. • Once-daily dosing for TDF (adults). • Less mitochondrial toxicity than other NRTIs. • Can give with food.	• No pediatric formulation of TDF. • Limited pediatric experience. • Potential for bone and renal toxicity; bone toxicity appears to be more frequent in younger children. • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.
ZDV ***plus*** d4T	• None.	• Pharmacologic and antiviral antagonism.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HSR = hypersensitivity reaction; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; PK = pharmacokinetic; TDF = tenofovir; TPV = tipranavir; ZDV = zidovudine

and neutropenia; minor toxicities include gastrointestinal (GI) toxicity and fatigue.

Both lamivudine and emtricitabine are well tolerated with few side effects. Although there is less experience in children with emtricitabine than lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine in combination with abacavir or zidovudine). The advantages of emtricitabine are that it can be administered once daily and it is available as an oral solution. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs; a modest decrease in susceptibility to abacavir and didanosine; and improved susceptibility to zidovudine, stavudine, and tenofovir[109-110].

Abacavir in combination with either lamivudine or emtricitabine in children (AI): Abacavir in combination with lamivudine has been shown to be as potent or, possibly, more potent than zidovudine in combination with lamivudine in both children and adults[111-112]. However, abacavir/lamivudine has the potential for abacavir-associated life-threatening HSRs in a small proportion of patients. In 5 years of follow-up, abacavir plus lamivudine maintained significantly better viral suppression and growth in children than did zidovudine plus lamivudine and zidovudine plus abacavir[112]. Abacavir hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA-B*5701 (see Appendix A: Pediatric Antiretroviral Drug Information); however, in the United States the prevalence of HLA-B*5701 is much lower in African Americans and Hispanics (2%–2.5%) than in whites (8%)[113]. Pretreatment screening for HLA-B*5701 before initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir HSRs in HIV-infected adults (from 7.8% to 3.4%)[114]. Before initiating abacavir-based therapy in HIV-infected children, genetic screening for HLA-B*5701 should be performed and children who test positive for HLA-B*5701 should not receive abacavir **(AII*)**.

Tenofovir in combination with either lamivudine or emtricitabine in children ≥ 12 years and Tanner Stage 4 or 5 (AI*): Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an investigational oral sprinkle/granule formulation[115-118]. The use of tenofovir in pediatric patients age 12 to <18 years was recently approved by the FDA based on data from 1 (unpublished) randomized study in 87 treatment-experienced subjects who were randomized to receive tenofovir or placebo plus optimized background regimen (OBR) for 48 weeks. Although there was no difference in virologic response between the two groups, the safety and PKs of tenofovir in children in the study were similar to those in adults receiving tenofovir.

Tenofovir in combination with lamivudine or emtricitabine is a preferred dual-NRTI combination for use in adolescents age ≥12 years and Tanner Stage 4 or 5. The fixed-dose combination of tenofovir and emtricitabine and the fixed-dose triple combination of tenofovir, emtricitabine, and efavirenz both allow for once-daily dosing, which may help improve adherence in older adolescents. In studies in adults, tenofovir when used with lamivudine or emtricitabine in combination with efavirenz had potent viral suppression for up to 3 years and was superior to zidovudine/lamivudine/efavirenz in viral efficacy[119-120]. In ACTG 5202, adults were randomly assigned to tenofovir/emtricitabine versus abacavir/lamivudine in combination with boosted atazanavir versus efavirenz (in factorial design). Among adults with screening HIV-1 RNA ≥100,000 copies per mL, the times to virologic failure and to first adverse event were both significantly shorter in patients randomly assigned to abacavir/lamivudine than in those assigned to tenofovir/emtricitabine. Results for patients with lower entry viral loads and for comparisons by assignment to efavirenz or boosted atazanavir are not yet available[121]. A study of 688 adults receiving lopinavir/ritonavir in addition to the randomized backbone of either tenofovir/emtricitabine or abacavir/lamivudine showed no difference in antiviral efficacy, safety, or tolerability at 48 weeks[122]. In nonrandomized studies, 48-week virologic efficacy of tenofovir/emtricitabine in combination with lopinavir/ritonavir was similar to that seen in trials with other dual-NRTI backbones in treatment-naive

Table 13. Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active ARV Combination Regimens (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
Entry Inhibitors	**Entry Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Entry Inhibitor Class Disadvantages:** • Rapid development of resistance with T-20. • CCR5 inhibitors ineffective against CXCR4 virus, mixed CCR5 and CXCR4 viral populations, or dual-tropic virus.
Use in Special Circumstances		
T-20	• Susceptibility of HIV to a new class of ARVs • Route of administration ensures adequate drug levels	• Twice-daily subcutaneous injections. • 98%–100% incidence of local injection site reactions. • Poor adherence and limited levels of success in adolescents because of local site reactions.
Insufficient Data to Recommend		
MVC	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Ineffective against CXCR4 or mixed/dual-tropic viral populations. • Limited data on pediatric dosing or safety. • No pediatric formulation. • Multiple drug interactions; different dosing depending on NNRTI or PI coadministered with MVC.

Key to Acronyms: ARV = antiretroviral; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; T-20 = enfuvirtide

Table 14. Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active ARV Combination Regimens

	Advantages	Disadvantages
General Issues		
Integrase Inhibitors	**Integrase Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Integrase Inhibitor Class Disadvantages:** • Limited data on pediatric dosing or safety.
Insufficient Data to Recommend		
RAL	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Limited data on pediatric dosing or safety. • Pediatric formulations are investigational. • Potential for rare systemic allergic reaction or hepatitis.

Key to Acronyms: ARV = antiretroviral; RAL = raltegravir

adults[123]. Also, no difference in virologic response was demonstrated in a meta analysis of combination regimens containing tenofovir or zidovudine. However, tenofovir-containing regimens demonstrated better immunologic response, adherence, and less resistance[124].

In some, but not all, studies, decreases in bone mineral density (BMD) have been observed in both adults and children taking tenofovir for 48 weeks[115-118, 125]. At this time data are insufficient to recommend use of tenofovir as part of a preferred regimen for initial therapy in infected children in Tanner

Stages 1–3, for whom the risk of bone toxicity may be greatest[115, 118]. (See Appendix A: Pediatric Antiretroviral Drug Information for more detailed pediatric information.) Renal toxicity has been reported in children and adults receiving tenofovir. In 1 single-center study, the rate of beta-2-microglobulinuria was higher in children receiving tenofovir (12 of 44 children) than in children receiving other ARV agents (2 of 48 children), although creatinine clearance (CrCl) did not differ between the groups[126]. Given the potential for bone and renal toxicity, tenofovir may be more useful for treatment of children in whom other ARV drugs have failed than for initial therapy of treatment-naive children. Numerous drug-drug interactions with tenofovir and other ARV drugs, including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir, complicate appropriate dosing of tenofovir.

Alternative Dual-NRTI Regimens

Alternative dual-NRTI combinations include zidovudine in combination with abacavir or didanosine **(BII)**, didanosine in combination with lamivudine or emtricitabine **(BI*)**, and tenofovir in combination with lamivudine or emtricitabine in adolescents ≥12 years and Tanner Stage 3 (as opposed to Tanner Stages 4 and 5, where this is a preferred dual-NRTI regimen) **(BI*)**. There is considerable experience with use of these dual-NRTI regimens in children, and in a large pediatric study the combination of zidovudine and didanosine had the lowest rate of toxicities[127]. However, zidovudine/abacavir and zidovudine/lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir/lamivudine in 1 European pediatric study[100, 112].

The combination of didanosine and emtricitabine allows for once-daily dosing. In a study of 37 treatment-naive children age 3-21 years, long-term virologic suppression was achieved with a once-daily regimen of didanosine, emtricitabine, and efavirenz; 72% of subjects maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy[40]. Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who must be fed frequently and may decrease medication adherence in older children because of the complexity of the regimen. A comparison of didanosine given with or without food in children found that systemic exposure was similar but with slower and more prolonged absorption with food[128]. To improve compliance, some practitioners recommend administration of didanosine without regard to timing of meals for young children. However, data are inadequate to allow a strong recommendation at this time, and it is preferred that didanosine be administered under fasting conditions when possible.

Dual-NRTI Regimens for Use in Special Circumstances

The dual-NRTI combinations of stavudine with lamivudine or emtricitabine in children of any age and tenofovir in combination with lamivudine or emtricitabine in adolescents age ≥12 years and Tanner Stage 2 are recommended for use in special circumstances. Stavudine is recommended for use only in special circumstances because the ARV is associated with a higher risk of lipoatrophy and hyperlactatemia than other NRTI drugs[129-131]. Children receiving dual-NRTI combinations containing stavudine had higher rates of clinical and laboratory toxicities than children receiving zidovudine-containing combinations[127]. In children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive tenofovir, stavudine may be preferred to zidovudine for initial therapy because of its lower incidence of hematologic toxicity.

Dual-NRTI Regimens Not Recommended for Use

Certain dual-NRTI drug combinations are not recommended. These include zidovudine plus stavudine because of virologic antagonism. The drug structure of emtricitabine is similar to lamivudine and the

same single resistance mutation confers cross resistance, so these drugs should not be used in combination. The dual-NRTI combination of stavudine/didanosine is also not recommended for use as initial therapy because of potentially greater toxicity. In small pediatric studies, stavudine/didanosine demonstrated virologic efficacy and was well tolerated[107-108, 132]. However, in studies in adults, stavudine plus didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine plus lamivudine[133-134]; additionally, cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy[129, 135]. Abacavir/didanosine, abacavir/tenofovir, and didanosine/tenofovir are not recommended as dual-NRTI backbones in initial therapy on the basis of insufficient data in children.

All-NRTI Regimens

Triple-NRTI regimens are attractive for use in HIV-infected pediatric patients as initial therapy because of the ease of administration, availability of palatable liquid formulations, demonstrated tolerance, and avoidance of many drug interactions. Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited; in small observational studies, response rates of 47%−50% have been reported[136-137]. In adult trials, these regimens have shown less potent virologic activity when compared with NNRTI- or PI-based regimens. Based on the results of these clinical trials, the Panel recommends that a three-NRTI-based regimen consisting of zidovudine plus lamivudine plus abacavir should be used only in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naive children (e.g., because of significant drug interactions or concerns related to adherence) **(BI*)**.

Following is a discussion of findings in clinical trials of triple-NRTI regimens.

Zidovudine + lamivudine + abacavir: The triple-NRTI combination of zidovudine + lamivudine + abacavir has been demonstrated to have equivalent virologic efficacy compared with indinavir-[138] or nelfinavir-containing regimens[139] but was inferior to an efavirenz-based regimen[28, 140]. In a study of this regimen in previously treated children, the combination showed evidence of only modest viral suppression, with only 10% of 102 children maintaining a viral load of <400 copies/mL at 48 weeks of treatment[141].

Other triple-NRTI regimens: Clinical trials in adults also have investigated triple-NRTI regimens consisting of stavudine + didanosine + lamivudine, stavudine + lamivudine + abacavir, and didanosine + stavudine + abacavir[142-143]. The virologic response to all these regimens was inferior to viral suppression achieved in comparator regimens. In addition, the M184V lamivudine drug-resistance mutation was seen more frequently in patients treated with triple-NRTI regimens containing lamivudine. Tenofovir + abacavir + lamivudine and tenofovir + didanosine + lamivudine demonstrate significantly increased rates of virologic failure and are not recommended[144-146]. The tenofovir + zidovudine + lamivudine combination demonstrated antiviral activity in adults; however, no comparative data are available and the regimen is not recommended[147].

Regimens Not Recomended for Initial Therapy of Antiretroviral-Naive Children

Not Recommended for Initial Therapy for Children Because of Insufficient Data

A number of ARV drugs and drug regimens are not recommended for initial therapy of ARV-naive children because of insufficient pediatric data **(AIII)**. These are summarized below.

Regimens containing three drug classes: Data are insufficient to recommend initial regimens containing agents from three drug classes (e.g., NRTI plus NNRTI plus PI). Although efavirenz plus nelfinavir plus one or two NRTIs was shown to be safe and effective in HIV-infected children with prior NRTI therapy, this regimen was not studied as initial therapy in treatment-naive children and has the potential for inducing resistance to three drug classes, which could severely limit future treatment options[41-43].

New agents without sufficient pediatric data to recommend use as initial therapy (Tables 13 and 14): At this time several new agents that appear promising for use in adults do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. These agents include maraviroc (a CCR5 antagonist), raltegravir (an integrase inhibitor), tenofovir (in children age <12 years), and etravirine and ripilvirine (both NNRTIs). Raltegravir is being evaluated in treatment-experienced children; however, PK, safety, and efficacy data are not yet available and no pediatric formulation is commercially available. In June 2008, FDA approved tipranavir boosted with ritonavir for use in treatment-experienced children age 2–18 years; however, data are insufficient to consider use of the agent for initial therapy.

Enfuvirtide, a fusion inhibitor, is approved for use in combination with other ARV drugs to treat children age ≥6 years who have evidence of HIV replication despite ongoing ART (i.e., treatment-experienced children on nonsuppressive regimens). The drug must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%). Currently, data are insufficient to recommend use of enfuvirtide for initial therapy of children.

Antiretroviral Drug Regimens that Should Never be Recommended (Table 9)

Several ARV drugs and drug regimens are not recommended for use in therapy of children or adults. These are summarized below. Clinicians should be aware of the components of fixed-drug combinations so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

The following regimens or regimen components should never be offered to HIV-infected children:

- A single ARV drug (monotherapy) **(AII)**
- Two NRTIs alone **(AI)**
- Certain dual-NRTI combinations as part of a combination regimen:
  - Lamivudine + emtricitabine because of similar resistance patterns and no additive benefit **(AIII)**
  - Zidovudine + stavudine because of virologic antagonism **(AII)**
- Dual-NNRTI combinations **(AI*)**
- Unboosted saquinavir, darunavir, or tipranavir **(AII*)**
- Atazanavir + indinavir **(AIII)**
- Certain NRTI-only regimens
- Tenofovir + didanosine + (lamivudine or emtricitabine) **(AI*)**
- Tenofovir + abacavir + (lamivudine or emtricitabine) **(AI*)**

Monotherapy: Therapy with a single ARV drug is not recommended for HIV treatment because monotherapy is unlikely to result in sustained viral suppression, leading to the development of viral resistance to the drug used and cross resistance to other drugs in the same drug class. However, use of zidovudine alone is appropriate for prophylaxis for the newborn infant born to an HIV-infected mother. In this setting, 6 weeks of monotherapy with zidovudine is recommended for the infant. In the event the infant is identified as HIV infected, zidovudine should be discontinued and standard triple therapy initiated[26].

In a child with treatment failure associated with drug resistance and persistent nonadherence, monotherapy using an interim "bridging" regimen of lamivudine alone may be considered. "Bridging" regimens have been reported to be effective in delaying immunologic decline in adults with failing combination therapy, often due to nonadherence[148-149]. Bridging regimens should not be considered as initial therapy and should only be used in the interim as the clinician works intensively with the patient and caregivers to improve adherence before initiating a new, suppressive combination ARV regimen (see Approach to the Management of Antiretroviral Treatment Failure).

Dual-nucleoside regimens alone: Dual-NRTI therapy alone is not recommended for initial therapy because it is unlikely to result in sustained viral suppression, leading to the development of viral resistance to the drugs being used and cross resistance to other drugs within the same drug class. For children who have achieved viral suppression on a previously initiated dual-NRTI regimen, it is reasonable to either continue on this therapy or to add a PI or an NNRTI to the regimen. However, a child remaining on a dual-NRTI regimen should be switched to a three or more drug combination if viral rebound occurs (see Antiretroviral Treatment Failure in Infants, Children, and Adolescents).

Certain dual-nucleoside backbone combinations: Certain dual-NRTI combinations (zidovudine + stavudine, emtricitabine + lamivudine) are not recommended for therapy at any time because of pharmacological antagonism or inferior virologic response. Emtricitabine should not be used in combination with lamivudine because the NRTIs share a similar drug structure and the same single resistance mutation (M184V) induces resistance to both drugs.

Dual NNRTIs: An adult study (2NN) demonstrated increased toxicity with the combination of nevirapine plus efavirenz[36].

Certain PIs: The combination of atazanavir plus indinavir has the potential for additive hyperbilirubinemia. Unboosted saquinavir, darunavir, and tipranivir have low bioavailablity and do not achieve adequate drug levels; therefore, they should not be used without ritonavir boosting.

Three-NRTI regimen of tenofovir + (didanosine or abacavir) + (lamivudine or emtricitabine): The triple-NRTI combinations of tenofovir with (didanosine or abacavir) plus (lamivudine or emtricitabine) have a high rate of early virologic nonresponse when used as initial therapy in treatment-naive adults and are not recommended as combination therapy for children at any time[144-146].

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